REMARKS

Status of the Claims

Claims 1, 4-7 and 10-12 are pending. Claims 1, 4-7 and 10-12 are rejected. No claims are amended herein.

The 35 U.S.C. §112, First Paragraph Rejection

Claims 4-6 and 10-12 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner states that although a copy of the receipt of the ATCC patent depository was enclosed along with the response, filed October 11, 2005, Applicants had not fully complied with all the requirements for a deposit of biological material. For instance, the Examiner states that Applicants had not provided a Declaration stating that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804. Additionally, the Examiner states that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository and the complete taxonomic description.

Applicants enclose a Declaration signed by Applicant's attorney stating that the biological material which has been deposited is the biological

material specifically identified in the application as filed along with this response. Applicants submit that in the Response filed October 11, 2005, Applicants had enclosed a copy of the ATCC Patent Depository receipt and had amended line 5 on page 23 of the instant specification to include deposit (accession) number, date of deposit, name and address of the depository and the complete taxonomic description. Accordingly, based on submission of the Declaration and remarks, Applicants respectfully request the withdrawal of rejection of claims 4-6 and 10-12 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §103 Rejections

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Sosnowski** *et al* (WO 98/40508) in view of **Muzykantov** *et al* (Am J Physiol 270: L704-713, 1996). Applicants respectfully traverse this rejection.

In response to Applicants' lack of motivation argument, the Examiner contends that in a §103 rejection, each of the cited reference does not have to teach every element of the claims and cites the following teachings of the references. **Muzykantov** *et al* teach that Mab 9B9 is a safe, specific and useful carrier for drugs targeting specifically to the pulmonary vascular endothelium after systemic administration and that the antibody is internalized by the endothelial cells both in vitro and in vivo and that it is not degraded intracellularly. **Sosnowski** *et al* teach that any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is

internalized following binding, including but not limited to antibodies to molecules on endothelial cells and that 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob.

Additionally, **Sosnowski** *et al* also teach the utilization of bispecific antibodies that recognize an Ad knob protein as well as the target cell-specific receptor to ablate endogenous adenoviral tropism. The modified re-targeted, tropism-modified adenoviral vector system would result in increasing targeting specificity to pulmonary vascular endothelial cells expressing angiotensin converting enzyme and reducing transgene expression in non-pulmonary vascular endothelial cells. Based on this, the Examiner states that an ordinary skilled artisan would have been motivated to carry out the modification recited in the instant claims.

Furthermore, in response to Applicants' lack of teaching or demonstration of construction of the instantly claimed vector arguments, the Examiner cites the following teachings of the references: **USPN 6,613,563** which is the same as **Sosnowski** et al (WO 98/40508) has claims drawn to a tropism-modified adenoviral vector system that specifically targets cells expressing a preselected receptor, wherein the adenoviral vector contains a tissue-specific promoter operatively linked to a nucleic acid molecule that encodes a gene product and wherein the gene product enhances cellular proliferation or cellular differentiation (claims 1-7 of the issued US patent). **Muzykantov** et al

demonstrated that the MAb 9B9 to angiotensin converting enzyme is a safe, specific and useful carrier for drugs targeting to the pulmonary vascular endothelium after systemic administration. Based on this, the Examiner states that it is unclear why the adenoviral vector resulting from the combined teachings of **Sosnowski** et al and **Muzykantov** et al would not be expected to be stable or would not effective. In view of teachings of the prior art references discussed herein, the Examiner has maintained the rejections of the claims. Applicants respectfully disagree with the Examiner.

Applicants reiterate that the targeting component of the modified adenoviral vector of the instant invention comprises an anti-Ad5 antibody taught by **Sosnowski** *at al* and an anti-angiotensin converting enzyme antibody taught by **Muzykantov** *et al*, which are linked via a bi-specific antibody conjugate in the instant vector. The examples in the instant invention not only teach the construction of such a vector but also demonstrate efficacy of the vector *in vitro* and *in vivo*.

Muzykantov *et al* teach that the anti-angiotensin converting enzyme antibody, MAb 9B9 can target drugs specifically to the pulmonary vascular endothelium after systemic administration and that the antibody is internalized by the endothelial cells. **Sosnowski** *et al* claim a tropism modified adenoviral vector system that specifically targets cells expressing a pre-selected receptor, comprising an antibody or a fragment thereof that binds an adenoviral

capsid protein, a targeting ligand that binds the preselected vector and containing a nucleic acid molecule that encodes a gene product under the control of a promoter (claim 1 of USPN 6,613,563). With regard to the use of bispecific antibodies, **Sosnowski** *et al* teach that the bispecific antibody is attached to the viral capsid protein on one end and a targeting ligand such as a polypeptides that bind specific receptors on the other end (background on bi-specific antibodies in USPN 6,613,563). There is no teaching or suggestion in **Sosnowski** *et al* to conjugate such bi-specific antibodies to antibodies specific to target cell receptor instead of a polypeptide that binds such a receptor.

One of the criteria to establish a prima facie case of obviousness states that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. **Muzykantov** *et al* do not express the need to combine the anti-angiotensin antibody with any other element to increase the efficacy of the vector. **Sosnowski** *et al* do not suggest conjugating the anti-Ad5 knob antibody to an antibody specific to the target cell receptor. In fact, given the efficacy of the vectors taught in the prior art references one of ordinary skill in the art would not feel it necessary to modify the vectors any further. Based on this, Applicant submits that there is no suggestion or motivation in the prior art references themselves or in the knowledge available to one of ordinary skill in the art to combine the reference teachings.

Furthermore, the construction of the instantly claimed vector would require inclusion of an element (a bi-specific antibody conjugate) in addition to the elements described in **Muzykantov** *et al* and **Sosnowski** *et al.* Neither **Muzykanotov** *et al* nor **Sosnowski** *et al* demonstrate or teach how to obtain such an element. Although **Sosnowski** *et al* merely mention use of bi-specific antibody in their disclosure, the bi-specific antibody taught by **Sosnowski** *et al* is conjugated to anti-Ad5 knob protein on one end and to a polypeptide targeting a cell surface receptor on the other end. Therefore, if one of ordinary skill in the art were to use a bi-specific antibody conjugate as claimed in the instant invention, one would have to first construct such a conjugate and examine the stability of the vector after the conjugation and also determine the efficacy of such vector. Thus, in the absence of the teachings of the instant invention, one would forced to engage in random, undue experimentation in an attempt to arrive at the claimed invention. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of rejections of claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. §103(a).

Claims 1, 4-7 and 10-12 remain rejected under 35 U.S.C. §103(a) as being unpatentable over **Reynolds** *et al.* (Mol. Ther. 2: 562-578, 2000) in view of **Sosnowski** *et al* (WO 98/40508). Applicants respectfully traverse this rejection.

In response to Applicants' lack of motivation arguments, the Examiner states that in a §103 rejection, each cited reference does not have to

teach every element of the claims. The Examiner then points to the following teachings of the prior art references: **Reynolds** *et al* disclose a targetable, injectable adenoviral vector for selective gene delivery to pulmonary endothelium *in vivo*, the vector comprises a bispecific antibody (MAb 9B9 conjugated to 1D6.14 anti-knob Fab antibody) that target Ad infection specifically to angiotensin-converting enzyme which is preferentially expressed on pulmonary endothelium. Such a vector when injected into rats resulted in at least 20-fold increase in both Ad DNA localization and luciferase transgene expression in the lungs compared to the untargeted vector and reduced transgene expression in the liver. **Reynolds** *et al* discuss further refinements to avoid nonspecific uptake of vector for optimal efficacy. **Sosnowski** *et al* discuss use of tissue specific promoters such as endothelial-specific promoters (VEGF-receptor promoter) for expression in wide variety of cells including endothelial and smooth muscle cells to attain extra margin of specificity.

In view of this, the Examiner states an ordinary skilled artisan would have been motivated to carry out the above modification because **Sosnowski** *et al* teach that the use of an endothelial specific promoters would provide an extra margin of specificity since it would avoid non-specific uptake and non-specific expression of a transgene in non-targeted cells *in vivo*. Additionally, an ordinary skilled artisan would have reasonable expectation of success in carrying out the above modification in light of the teachings of the prior art references coupled with high levels of skill of an ordinary artisan in the art of making the vectors.

Hence, the Examiner has maintained the rejections of these claims. Applicants respectfully disagree with the Examiner.

Applicants reiterate that although **Reynolds** *et al* mention that further refinements may be required to avoid non-specific uptake of vector by reticuloendothelial system, they do not specify the refinements. There could be various reasons that could limit the use of the vector discussed in **Reynolds** *et al* (page 4, line 10-page 5, line 7 of the instant invention). **Reynolds** *et al* also admit that there is a paucity of data concerning true targeting in vivo (page 577, 1st col, last para.).

Furthermore, although **Sosnowski** *et al* teach the use of tissue specific promoters for expression in endothelial and smooth muscle cells, they do not demonstrate the use of these promoters in their constructs. Therefore, although the combined teachings of the two references may motivate one of ordinary skill in the art to use such promoters in their constructs, one may still be trying to arrive at the claimed invention since there is lack of understanding of the exact reason limiting the use of the vector taught by **Reynolds** *et al*. It has long been established that trying is not a standard for obviousess. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of rejection of claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. §103(a).

This is intended to be a complete response to the Office Action mailed August 18, 2006. Applicants enclose a Declaration, a Petiton for Extension of Time (3months) and Form PTO-2038 along with the Response. Applicants submit that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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